REMARKS

Reconsideration of the application is requested in view of the amendment to the claims and the remarks presented herein.

The application has been amended to insert reference to the parent application and the PCT application and the claims have now been properly amended.

Claims 1 to 16 have been rejected as improperly recapturing subject matter surrendered in the parent application to obtain issuance thereof. The Examiner is of the opinion that the rejection of the claims was withdrawn because Applicants'amendment did not include the presently claimed subject matter. The Examiner further contends that Applicants gave up the claimed subject matter whether intentional or not.

Applicants traverse this ground of rejection since the claims during prosecution were not limited to avoid any prior art rejection but was the result of an amendment error. As pointed out in the declaration in the preliminary amendment of July 23, 1999 that the claims were inadvertently and without deceptive intent were inadvertently to the quinoline compounds which was not intended and was not necessary to avoid prior art since claim 2 of the issued patent claims subject matter which was not within the scope of claim 1 shows that the subject was not intended to be cancelled from the application.

Applicants are submitting herewith for the Examiner's convenience the following documents from the issued patent file:

- a copy of the Office Action of August 16, 2000;
- a copy of the response of August 29, 2000;
- a copy of the Office Action of December 13, 2000;
- a copy of the Office Action of January 20, 2001;
- a copy of our instructions of March 15, 2001, and March 19, 2001, wherein claim 1 mentioned residues than can be protonated belonging to the family of compounds which carry an imidazole nucleus, to the family of quinolines, to the family of pterines, and to the family of pyridines; and
- a copy of the amendment of July 17, 2001, wherein amended claim 1 was limited to residues belonging to the family of quinolines.

The narrowing of the claims was in error, and not a voluntarily abandonment, as shown by some inconsistencies between claims such as issued. When residues causing destabilisation of cell membrane in a weakly acid medium are restricted to quinolines, as in claim 1 of US 6,372,499, there is an inconsistency with claims 8 and 9, because claims 8 and 9 relate to complexes wherein the residues causing destabilisation of cell membrane in a weakly acid medium contain an imidazole nucleus. These inconsistencies are not observed when said claim 1 is modified so as to include "family of compounds having an imidazole nucleus, pterines, pyridines and quinolines".

One of the unexpected results of the present invention is that the polylysine substituted with different residues is able to destabilize cell membranes in an acidic medium when it is complexed with a nucleic acid. Indeed, such protonated residues

(including but not limited to histidine) would be expected to interact with the phosphate group of the nucleic acid as described for the copolymer Poly(LysHis) in the copolymer / DNA complexes (Santella R.M., Li H.J., 1997, Interaction between poly(L-Lysine, L-Histidine) and DNA, Biopolymers 16, 1879-1894) and therefore, they were not expected to be able to interact with cell membranes in order to induce their destabilization. The inventors compared the percentage of transfection using polylysine substituted with different residues. (see annex: Experimental results table 1 and figures 10 to 18 for answer to Office Action of January 18, 2001).

Therefore, it is believed clear that the claims were not limited to avoid prior art but due to a mistake by the attorney's secretary not caught by him and withdrawal of this rejection is requested.

Claims 1 to 15 were rejected under 35 U.S.C. 103 as being obvious over French Patent A271316 as the Midoux patent taken in view of Wang et al. The Examiner argues that one skilled in the art would expect that Wang's demonstration that Wang is merely an expected result and that Wang is not used done but in combination with other art.

Applicants respectfully traverse this ground of rejection as the combination of the prior art made by the Examiner with the benefits of Applicants'teaching would not teaching would not teach Applicants'invention. The Midoux et al patent discloses a compound that could be used for cell transfection, consisting of polylysine wherein at least one free amino function is substituted with non-charged residues and at least one said free amino function is substituted with recognition signals, the conjugated polylysine containing at least 30% unsubsituted free amino function. Said substituted polylysine

allows (col. 3, lines 27-38): I) the formation of stable complexes with a negatively charged nucleic acid, and ii) the facilitation of the dissociation of the complex and the release of the nucleic acid: the substitution of NH_3^+ by non-charged residues possessing less positive charges reduces the interaction cooperativity and facilitates the dissociation between the DNA and the polymer (col. 3, l. 43-46). The presence of recognition signal is to render the transfection selective for different types of cells, and to make the transfection effective *in vivo*. Midoux does not address the critical step of transmembrane passage for plasmid DNA, from the endosome into the cytosol, and the importance of membrane destabilisation, which is central to the invention disclosed in the present application (col. 2, l. 16-19).

The teaching of Wang et al. belongs to the field of membrane fusion. Wang et al. discloses a linear polyhistidine polypeptide and shows that at acid pH (beow 6.5) the protonation of histidine residues destabilizes phosphatidylserine liposomes, which leads to liposomes fusion. The authors propose that, at reduced pH, polyhistidine becomes a polycation and aggregates the negatively charged liposomes (Wang et al. p. 4414, right column) and does not disclose nor suggest the association of any nucleic acid to said polymer, nor the question of transfecting nucleic acid into cells. A person skilled in the art of cell transfection, wishing to raise cell transfection efficiency, would have not combined the teaching of Midoux, et al. with Wang, et al., as these documents do not relate to the same field. The combination of these two documents is an a posteriori analysis of the obviousness of an invention, although such analysis should be avoided.

The French reference describes a substituted polylysine with non-charged residues so as to lower its positive charges, whereas Wang et al. disclose the effect of polyhistidine on membrane fusion due to its positive charge. Therefore, Midoux, et al and Wang, et al go to opposite directions and should not be combined. Although highly improbable, should the person skilled in the art have combined the teaching of Midoux, et al with the teaching of Wang, et al, he/she would have to make undue experimentation to determine if the positive charges from histidine disclosed in Wang, et al. interact with 1) the negative charges of the nucleic acid, and in that case the efficiency of membrane destabilisation should strongly diminish as compared with efficiency measured in Wang, et al when there is no nucleic acid, or 2) with the negative charges of the cellular membranes. The inventors have confirmed that , surprisingly, the positive charges of histidine do not interact with negative charges of nucleic acid (Bello-Roufai and Midoux, 2001, Bioconjucate Chem., Vol. 12, pages 92-99, enclosed). Furthermore, the effective fusion of liposomes disclosed in Wang, et al would not allow a person skilled in the art to be confident to destabilize living cell membranes, as does the present invention.

Therefore, the combination of the prior art does not render obvious Applicants' invention and withdrawal of this rejection is requested.

For the Examiner's information, Applicants are submitting herewith copies of the claims granted in the European and Australian Applicants corresponding to the issued United States Patent for the Examiner's convenience. The main claims of these patents protect residues causing membrane destabilization being possibly "compounds having an imidazole nucleus, pterines, pyridines and quinolines."

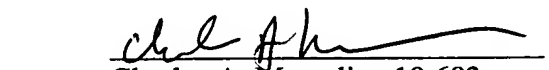
With respect to the obviousness type double patenting rejection based on the claims of U.S. Patent No. 5,733,762, Applicants are herewith a terminal disclaimer with respect to the Patent which obviates this ground of rejection.

Claim 2 was rejected under 35 U.S.C. 112, second paragraph as being drawn to a confusing structure with respect to the quinolines and other members of the Markush group.

Applicants are willing to rewrite claim 2 in independent form after the resolution of the question of the issue of the recapture issue and it is requested that this ground of rejection be held in abeyance until then. The same request is made for the rejection of claims 1 to 16.

In view of the amendment to the claims and the above remarks, it is believed that the rejections should be withdrawn. Therefore, favorable reconsideration of the application is requested.

Respectfully submitted,
Hedman and Costigan



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Enclosures